SHORT REPORT

Type 1 Diabetes Mellitus and Down's Syndrome: Prevalence, Management and Diabetic Complications

A.J. Anwar, J.D. Walker*, B.M. Frier

Department of Diabetes, Royal Infirmary of Edinburgh, NHS Trust, Edinburgh

Type 1 insulin-dependent, diabetes mellitus (Type 1 DM) is thought to be more prevalent in individuals with Down's syndrome. To ascertain the local prevalence of Type 1 DM in patients with Down's syndrome in a geographically defined area, the four diabetes clinics in Lothian were surveyed and 13 patients with Down's syndrome and Type 1 DM were identified. Using data from previous epidemiological surveys which determined the prevalence of Down's syndrome in the general population, the prevalence rate of Type 1 DM in patients with Down's syndrome was calculated to be between 1.4 and 10.6 %, a prevalence considerably higher than in the general population. Although 7 (54 %) of the Down's syndrome patients were treated with once daily administration of insulin, the mean HbA_{1c} value of the group was similar to that observed in a control group of 39 age-, sex- and duration-matched Type 1 patients, all of whom were taking two or more injections of insulin daily. Glycaemic control was therefore of similar quality to matched Type 1 patients without Down's syndrome, despite the frequent use of simple insulin regimens, which may relate to the more stable lifestyle of these patients.

***Diabet. Med.* 15: 160–163 (1998)**

KEY WORDS **Down's syndrome; insulin-dependent diabetes mellitus; insulin; diabetic complications**

Received 20 August 1997; accepted 21 September 1997

Introduction

The clinical characteristics of Down's syndrome, namely short stature, bracycephaly, typical facies, clinodactyly and Brushfield spots, were first described in 1866 by John Langdon Down.[1] The chromosomal abnormality was identified in 1959 and 95 % of cases are associated with trisomy of chromosome 21. Some authors have suggested that the prevalence of diabetes mellitus is increased in patients with Down's syndrome[2,3] but this has been disputed.[4] The aim of the present study was to investigate the prevalence of Type 1, insulin dependent, diabetes mellitus (DM) in Down's syndrome in a geographically defined population; to evaluate the management regimens and the quality of glycaemic control achieved and to ascertain whether these patients had diabetic complications and other medical disorders.

Methods

Case Identification

The five hospital diabetes clinics in Lothian (Royal Infirmary of Edinburgh (RIE), Western General Hospital, Royal Hospital for Sick Children (RHSC), Eastern General Hospital (EGH), all in Edinburgh, and St John's Hospital at Howden were surveyed. Patients were identified from a computerized clinical database where this facility was available (RIE) and by interviewing relevant staff members at each clinic. No patient with Down's syndrome and Type 1 DM was found to be attending RHSC and the EGH. The medical records of all identified patients were reviewed to obtain demographic details, current treatment regimens, physical features, established diabetic complications, other medical disorders and recent clinical and biochemical profiles. Type 1 diabetes was defined as ketosis-prone diabetes, requiring treatment with insulin at or within 1 month of diagnosis and with age of onset before 40 years of age (in all but one case). All cases of Down's syndrome had been diagnosed in infancy by clinical examination, and a confirmatory chromosomal analysis had been performed in two patients.

Blood pressure values, recorded at three consecutive annual review visits at the diabetes outpatient clinic, were used to derive a mean value for each patient. The mean value of all recorded estimations of glycated haemoglobin (HbA_{1c}) concentration (measured with an HPLC method using a Diachii Biomen analyser) over the last 3 years was calculated for each patient. Mean values of total plasma cholesterol, HDL-cholesterol and triglyceride concentrations were calculated from results from the preceding 3 years. No data on plasma lipids were available on one patient. Body mass index recorded at the most recent clinic attendance was used for analysis.

* Correspondence to: Dr J.D. Walker, Department of Diabetes, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW, UK

 CCC 0742–3071/98/020160–04$17.50

Either the patients, or their carers, or both, were interviewed using a structured questionnaire, either personally, or by telephone, to record details of current insulin regimens and dosage, methods of administration of insulin and details regarding the frequency, if any, of home capillary blood glucose monitoring.

Type 1 DM Control Cases Without Down's Syndrome

A cohort of 39 age-, sex- and duration-matched Type 1 DM patients attending the diabetic clinic at the RIE were selected from the clinic database to act as control cases. Details of insulin regimens and doses, values of HbA_{1c}, blood pressure and plasma lipids for these patients were obtained from their case notes, in a similar manner to the patients with Down's syndrome. No patients were taking anti-hypertensive medication.

Prevalence of Down's Syndrome in Lothian

Two previous epidemiological surveys estimated the prevalence of Down's syndrome locally in Lothian and in the United Kingdom.[5,6] Murdoch[5] used a postal survey to identify patients with Down's syndrome registered with 1138 general practitioners (GP) in Scotland, while Steele and Stratford[6] contacted representatives of a large number of health authorities and social services departments in the UK to obtain information on individuals registered as having Down's syndrome in 1987.

Statistics

In an attempt to correct for the accuracy of the previous estimates of the prevalence of Down's syndrome in Lothian, the Fleiss calculating formula for 95 % confidence intervals of proportions was employed.[7] The population of Lothian was taken from the General Register for Scotland, 30th June 1994, for this. The Fleiss calculation was also used to estimate the prevalence of Type 1 DM in Down's syndrome.

Results

The two previous epidemiological surveys estimated the prevalence of Down's syndrome in Scotland[5] and the U.K.[6] to be between 0.03–0.07 %. Applying this prevalence to the population of Lothian (758 600 in June 1994) and correcting these values using the Fleiss calculating formula, we calculated that between 199 and 578 individuals with Down's Syndrome should reside within Lothian. Thirteen patients with Down's syndrome and Type 1 DM were identified, giving an estimated prevalence of between 1.4 and 10.6 % for Lothian, assuming no patient with Down's syndrome and Type 1 DM was receiving care solely from a general practitioner and case ascertainment was complete. The demographic details of the 13 diabetic patients with Down's syndrome and the 39 control diabetic patients are shown in Table 1. The subjects were well matched for age, age at diagnosis of diabetes and duration of diabetes and there was no significant difference in daily insulin dose. All 39 control Type 1 DM patients injected insulin at least twice a day.

Eight of the 13 patients (62 %) were being cared for either in residential homes or in long-term hospital care. A single daily injection of insulin was administered in 7 of the 13 patients (54 %). The person who administered the insulin was determined partly by the place of residence of the patient: family members administered insulin to 4 of the 5 patients who were living in their family home while district nurses or residential home staff were responsible for administering insulin to 6 of the 8 patients in residential care or long-term hospital care. Three patients self-administered their own insulin although the insulin was drawn up and measured by a district nurse. All patients had a capillary blood glucose concentration measured at least once daily.

Clinical and biochemical profiles of the Down's syndrome patients and the controls are shown in Table 2. Plasma cholesterol and systolic blood pressure were significantly lower in the Down's patients. Their higher BMI was not significant. Two Down's syndrome patients (15 %) had documented diabetic complications with coexisting nephropathy and peripheral neuropathy, one of whom was also blind as a result of proliferative diabetic retinopathy. This patient died shortly after the survey was completed having elected to cease haemodialysis for chronic renal failure due to diabetic nephropathy. Five patients (38 %) had coexisting primary hypothyroidism and were taking thyroxine replacement therapy.

Discussion

The prevalence of Type 1 diabetes mellitus in the UK population is estimated to be between 0.18 and 0.30 %.[8–10] In patients with Down's syndrome in Lothian the

Table 1. Demographic details of patients with Down's syndrome and Type 1 diabetes mellitus (results expressed as median (range))

	Down's syndrome patients with Type 1 DM (n = 13)	Control non-Down's syndrome patients with Type 1 DM (n = 39)
Age (yr)	37 (27–55)	38 (23–58)
Gender (F:M)	9:14	27:12
Age at diagnosis of DM (yr)	22 (5–42)	20 (4–42)
Duration of DM (yr)	15 (2–34)	16 (2–38)
Insulin dose (U kg^{-1})	0.59 (0.33–1.25)	0.65 (0.17–1.1)

Table 2. Biochemical and clinical parameters of patients with Down's syndrome and Type 1 DM and control Type 1 DM group (results expressed as mean ± SD)

	Down's syndrome patients with Type 1 DM (n = 13)	Control patients with Type 1 DM (n = 39)
HbA_{1c} (%)	7.8 ± 1.0	7.5 ± 1.5
Cholesterol (mmol l^{-1})	4.5 ± 1.0	5.3 ± 1.1[a]
HDL Cholesterol (mmol l^{-1})	1.5 ± 0.6	1.5 ± 0.4
Triglycerides (mmol l^{-1})	1.2 ± 0.5	1.3 ± 0.7
Body mass index (kg m^{-2})	28.2 ± 4.7	25.6 ± 3.8
Blood pressure		
Systolic (mmHg)	113 ± 15	128 ± 14[b]
Diastolic (mmHg)	70 ± 9	75 ± 9

[a]$P < 0.02$; [b]$P < 0.01$.

prevalence of Type 1 DM determined from the present study lies between 1.4 and 10.4 %, suggesting a 10 fold increase in prevalence compared to the general population. A propensity to develop autoimmune disorders is well described in patients with Down's syndrome, although previous investigations have focused on autoimmune disorders affecting the thyroid gland.[11] In the present study the prevalence of hypothyroidism was higher in the patients with Down's syndrome and diabetes compared to Type 1 diabetic patients from our clinic without Down's syndrome,[12] although not as high as recently reported in a smaller sample of patients with Down's syndrome and Type 1 DM.[13] The association of Down's syndrome with Type 1 DM and hypothyroidism suggests a common genetic susceptibility to an autoimmune process. Although a number of studies have suggested that genes in the HLA-D region of chromosome 6 are important in the susceptibility to Type 1 DM[14–16] recent work has pointed to chromosomal locations outside the major histocompatibility locus that also confer susceptibility.[17] Interestingly, chromosome 21 does not appear to have a strong association with the development of Type 1 DM.

The median age for the development of Type 1 DM in patients with Down's syndrome was higher than that reported in earlier studies but this may have been influenced by the predilection of previous studies to survey paediatric populations.[2,3] All but one of the patients with Down's syndrome in the present series developed diabetes after the age of 10 years. The life expectancy of people with Down's syndrome has increased from a total of less than 10 years in the 1930s to survival into the late teens in the 1960s and more recently to over the age of 50 years thereby allowing a greater period of time for Type 1 DM to become clinically manifest.[6] Thus, the altered natural history of Down's syndrome in the modern era may be unveiling the presentation of diabetes in young adults. Whereas in the non-diabetic Down's population there is an excess of males,[5] the present study confirms the trend suggested by a previous study showing that the normal male predominance is reversed in those who develop diabetes.[2]

Our study relied on personal recall and was clinic-based. A population-based survey employing capture/recapture methodology would be an ideal study design. However, we are confident that the search codes we used to interrogate our database will have identified all patients with Type 1 DM and Down's syndrome and such patients are likely to be accurately recalled by diabetes specialist staff where computerized databases were not available. We did not survey patients with Down's syndrome and Type 2 diabetes as we felt that a number of such patients may be receiving GP-only care and case ascertainment in this group may be incomplete. Another potential problem with our survey was the use of the two previous estimates of Down's syndrome which were applied to the population of Lothian. One survey included Lothian and the prevalence of Down's syndrome in Lothian was the same as the mean for the whole survey population. Maternal age could have an influence on the prevalence of Down's syndrome in the general population. Maternal age-specific Down's syndrome incidence rates were corrected for mortality providing an overall prevalence in one of the sources used[6] and data from the General Register Office for Scotland reveals that the modal maternal age range for childbirth has remained at 25–29 years for each 5-year interval since 1946 until 1995 except for the years 1961 to 1975 when the modal maternal age-range for childbirth fell to 20–24 years. The reduction in maternal age for childbirth in Scotland between 1961 and 1975 may have resulted in a reduction in the number of children born with Down's syndrome and if anything we may have overestimated the number of cases of Down's syndrome in Lothian which in turn would result in an even higher prevalence of Type 1 DM in this population.

Administration of a once daily injection of insulin provides a convenient way of providing insulin therapy to a group of individuals with variable levels of disability who are dependent on others for their medication. Although this regimen is often associated with suboptimal glycaemic control, in the diabetic patients with Down's syndrome the glycated haemoglobin level was comparable to that of Type 1 diabetic controls. Most of the patients with Down's syndrome were leading stable and often institutionalized lifestyles, which may have assisted in the maintenance of stable glycaemic control, particularly with respect to diet and compliance. In achieving reasonable glycaemic control on a regimen of insulin administered once daily, it is possible that unrecognized asymptomatic hypoglycaemia may be occurring, although no evidence of biochemical hypoglycaemia was identified from home blood glucose monitoring.

The lower concentration of plasma cholesterol in the patients with Down's syndrome is a novel finding. Total plasma triglyceride levels have been reported to be higher in non-diabetic Down's syndrome patients[18,19]

Diabet. Med. 15: 160–163 (1998)

but this was not observed in our patients, possibly as a consequence of the effects of insulin on lipid metabolism. Systolic blood pressure was also lower in the Down's syndrome patients, despite their tendency to a high body mass index. Our data may suggest that Down's syndrome offers some protection against atherosclerosis, unrelated to plasma lipid profiles, as there was little recorded evidence of diabetic complications and macrovascular disease in the present study. However, screening for diabetic complications may be difficult in diabetic patients with Down's syndrome and our cohort is too small to provide an accurate estimate of the incidence of micro- and macrovascular complications.

In conclusion a high prevalence of Type 1 DM has been observed in patients with Down's syndrome in Lothian. Glycaemic control did not differ from that of a matched cohort of non-Down's syndrome patients with Type 1 DM despite differences in diabetic management.

Acknowledgments

We thank R.S. Gray, J.A. McKnight, C.J. Kelnar, and A.W. Patrick who kindly allowed access to case records and to individual patients under their care, and the assistance of the patients, carers and paramedical staff in diabetes clinics of Lothian.

References

1. Down JL. Observations on an ethnic classification of idiots. *London Hospital Reviews* 1866; **3**: 259–262.
2. Milunsky A, Neurath PW. Diabetes mellitus in Down's syndrome. *Archives of Environmental Health* 1968; **17**: 373–376.
3. Farquhar JW. Diabetic children in Scotland and the need for care. *Scot Med Journal* 1962; **7**: 119–124.
4. Schoffling K, Schade C. Diabetes mellitus and impaired glucose tolerance in diseases with chromosomal aberrations. In: Creutzfeld W, Kobberling J, Neel JV, eds. *The Genetics of Diabetes Mellitus*. Berlin: Springer Verlag, 1976: 125–137.
5. Murdoch J. A survey of Down's syndrome under general practitioner care in Scotland. *J Roy Coll Gen Pract* 1982; **32**: 410–418.
6. Steele J, Stratford B. The United Kingdom population with Down's syndrome: present and future projections. *American Journal of Mental Retardation* 1995; **99**: 664–683.
7. Fleiss JL. *Statistical Methods for Rates and Proportions*, 2nd edn. New York: Wiley, 1981: 14–17.
8. Gray A, Fenn P, McGuire A. The cost of insulin-dependent diabetes mellitus (IDDM) in England and Wales. *Diabetic Med* 1995; **12**: 1068–1076.
9. Neil AW, Gatling W, Mather HM, Thompson AV, Thorogood M, Fowler GH, *et al*. The Oxford Community Diabetes Study: evidence for an increase in the prevalence of known diabetes in Great Britain. *Diabetic Med* 1987; **4**: 539–543.
10. Bingley PJ, Gale EAM. Incidence of insulin dependent diabetes in England: a study in the Oxford region. *Br Med J* 1989; **289**: 558–560.
11. Kennedy RL, Jones TH, Cuckle HS. Down's syndrome and the thyroid. *Clin Endocrinol* 1992; **37**: 471–476.
12. Perros P, McCrimmon RJ, Shaw G, Frier BM. Frequency of thyroid dysfuction in diabetic patients: value of annual review. *Diabetic Med* 1995; **12**: 622–627.
13. Griffin ME, Fulcher T, Nikookam K, Crowley J, Firth RG, O'Meara NM. Down's syndrome, IDDM, and hypothyroidism. *Diabetes Care* 1997; **20**: 1202–1203.
14. Rich SS. Mapping genes in diabetes. *Diabetes* 1990; **39**: 1315–1319.
15. Gorsuch A. The immunogenetics of diabetes. *Diabetic Med* 1987; **4**: 510–516.
16. Keen H. The genetics of diabetes: from nightmare to headache. *Br Med J* 1987; **294**: 917–918.
17. Todd JA, Aitman TJ, Cornall RJ, Ghosh S, Hall JRS, Hearne CM, *et al*. Genetic analysis of autoimmune type 1 diabetes mellitus in mice. *Nature* 1991; **351**: 542–547.
18. Nishida Y, Akaoka I, Nishizawa T, Maruki M, Maruki K. Hyperlipidaemia in patients with Down's syndrome. *Atherosclerosis* 1977; **26**: 373–377.
19. Pueshell FM, Craig WY, Haddow JE. Lipids and lipoproteins in persons with Down's syndrome. *J Intell Disabil Res* 1992; **36**: 365–369.

